

Endocrine

Diabetes mellitus

Definition

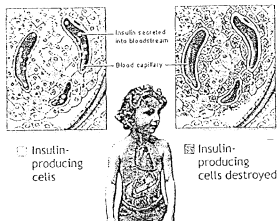
- It is a chronic metabolic disorder caused by relative or absolute deficiency of insulin

The Greek word Diabetes = to Siphon / pass through

Classification

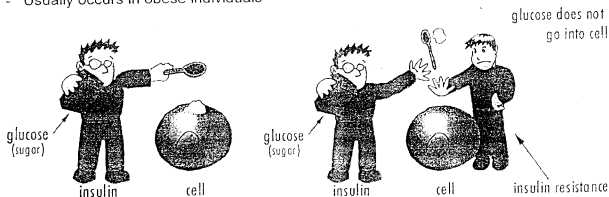
1. Type 1

- IDDM : There is absolute deficiency of insulin → partial, complete



2. Type 2

- NIDDM : here the insulin level is normal but the problem is in the response to insulin.
- Serum concentration of insulin may be normal or moderately depressed
- The onset of the disease occurs after the age of 40 years
- It is rare in childhood and adolescence
- Usually occurs in obese individuals



3. Type 2 in pediatric age :

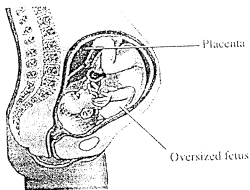
- Maturity onset diabetes of young (MODY) → which like NIDDM but in young age.
- In this type of diabetes there is strong family history of type 2 DM in pattern suggestive of AD inheritance.
- In this type there is no association with HLA, autoimmunity or islet cells Abs.

4. 2ry DM associated with other diseases :

- Pancreatic diseases
- Endocrine diseases : Cushing , $\uparrow$ GH , & steroid therapy
- Genetic diseases : Down , Prader- Willi syndrome
- Insulin receptor abnormalities

5. Gestational DM

- Occurs in pregnant females.



Etiology of IDDM:

It is not inherited so that family history of DM is not important but it is determined by :

1) Genetic predisposition :

- o A higher incidence of IDDM is observed in association with HLA-DR3 , -DR4 , - B8 & B15.

2) Autoimmune response :

- o Both humoral & cellular mediated response were observed early in the course of disease in most patients with IDDM .
- o Autoimmune response $\rightarrow$ production of Abs either:
 - i. Anti-B cell Abs : " islet cell Abs"
 - ii. Anti-Insulin Abs

3) Environmental factors :

- o Early exposure to cow milk feeding : may be a factor in triggering DM , so DM is lower in breast feed infants .
- o Viruses : " mumps , measles , coxsackie-B2,4&5 " $\rightarrow$ initiate IDDM in genetically predisposed individuals

These infections act by 2 mechanisms :

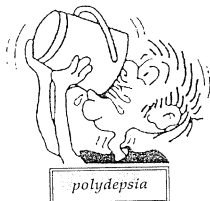
- i. Autoimmunity
- ii. Change the antigenecity of the cells

Epidemiology of IDDM:

- Sex: both are equally affected
- Age of presentation : 5-7 years & at puberty
- Season : Autumn & Winter
- There is definite increased incidence of diabetes in children with congenital rubella
- Prevalence of IDDM is about 0.2-1.2 in 1000 in Egypt & all over the world .

CP:

- Asymptomatic : accidentally discovered
- Classic manifestations: polyuria , polydipsia , polyphagia & wt loss .
- 2ry nocturnal enuresis
- Symptoms of complications :
 - 1) Recurrent multiple skin infections e.g monilial vulvo-vaginitis in females:
 - 2) Keto-acidosis in 30 %
 - 3) Hypoglycemia $\rightarrow$ in case of insulin overdose.



Investigations :

A. For a newly diagnosed patient :

1. Urine : glucosuria $\pm$ Ketone bodies .
2. Fasting blood glucose : $\uparrow \uparrow > 125 \text{ mg/dl}$ "N : $60-110 \text{ mg/dl}$ "
3. Glucose tolerance test "in doubtful cases "
 - The fasting child ingests 1.75 gm / kg glucose in 5 min "maximum = 75 gm total"
 - Blood samples are taken at 0 , 30 , 60 , 120 min . for glucose determination.
 - If 2 hours value & one hour value are more than 200 mg/dl = DM.



4. Serum insulin determination & C-Peptide by radio-immune assay :
 - to differentiate between type 1 & 2.
5. Islet cell antibodies (ICA) :
 - in 80-90 % of newly diagnosed type 1DM
 - The prevalence of these antibodies decrease with the duration of established disease.
6. Anti-insulin antibodies :
 - in 30-40 % of newly diagnosed type 1DM.

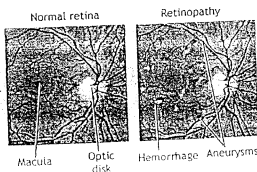
B. For follow up :

1. Daily blood glucose monitoring (self monitoring)
2. Intermediate monitoring every 2-4 weeks by fructosamine .
3. Long term follow up / 3 months by glycosylated Hb "Hb-A1c" .
 - it is formed by an irreversible slow reaction between the N-terminal of beta globin chain of Hb & glucose.
 - Since the life span of RBCs is 120 days $\rightarrow$ so glycosylated Hb is expected to reflect the mean blood glucose concentration in the last 2-3 months.
4. Every year the following are done :
 - 1) Blood urea & serum creatinine .
 - 2) ALT , AST & Alkaline phosphatase.
 - 3) Cholesterol , lipoproteins , HDL & LDL.
 - 4) T3, T4 & TSH
 - 5) Fundus examination after 5 years of onset of micro albumin in urine.

Complications :

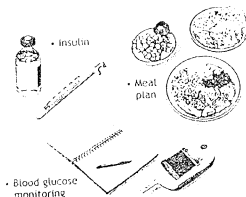
1. $\downarrow\downarrow$ immunity
 - 1) $\uparrow\uparrow$ susceptibility to infections
2. Coma
 - 1) DKA
 - 2) Lactic acidosis
 - 3) Hyperosmolar non ketotic
 - 4) Hypoglycemia
3. Growth retardation + hepatomegaly

Moriac syndrome
4. Long term complications:
 - 1) Neuropathy $\rightarrow$ sensory > motor & LL > UL.
 - 2) Nephropathy
 - 3) Retinopathy & cataract
 - 4) Cerebrovascular accidents
 - 5) Myocardial infarctions.
 - 6) Arthropathy.



Lines of treatment :

- 1) Diet
 - 2) Exercise
 - 3) Insulin
 - 4) Psychological
 - 5) Health education
 - 6) Home glucose monitoring
- ❖ Aims of treatment :
1. Control of hyperglycemia .
 2. General health maintenance.
 3. Psychological & emotional satisfaction.



A. Diet

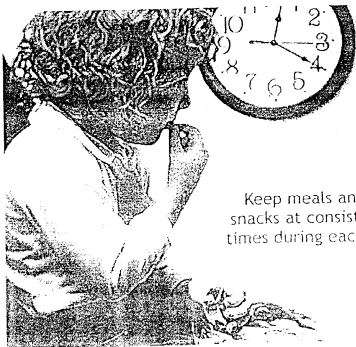
- The major goals of dietetic management are :
 - To ensure the pattern of growth and maturation that simulate the pattern of healthy non diabetic children.
 - Help the control of wide fluctuation of blood glucose.
- Dietetic management is essential in treatment of DM → usually it is difficult below 5 years.
- Above 5 years :
 - An adequate total caloric intake should be given to support adequate growth.

$$\text{The total amount} = 100 \times \text{age " years " } + 1000 \text{ calories.}$$
 - Adequate diet should contain :

55 % CHO	30 % Fat	15 % Proteins	Vitamins
- Highly refined sugars should be avoided	- Vegetable sources are better. - ↓↓Cholesterol.		- Esp . B complex.

- The total daily caloric intake can be divided as follow " 3 meals + 2-3 mid-meal snacks "
 - 20% in breakfast
 - ❖ 10 % mid morning snack.
 - 20% in lunch.
 - ❖ 10% mid afternoon snack
 - 30 % in dinner.
 - ❖ 10 % evening snack.
- Meals and snacks should be kept at constant time each day.

- Diet with high fiber contents are useful in control of blood glucose in DM.**
- Fruits : can be given, but no grapes, mangoes or nuts.**
- Artificial sweeteners as saccharin & aspartame may be carcinogenic .**



Keep meals and snacks at consistent times during each day

B. Exercise :

- It reduce the amount of required insulin.
- However the caloric contents of snacks should be increased for fear of hypoglycemia.
- It should be :

1. Non- competitive : due to $\uparrow\uparrow$ epinephrine secretion in competition.
2. Not causing stress or fatigue.
3. If hypoglycemia occurs $\rightarrow$ orange juice or sugars should be available.

❖ **Advantages of exercise :**

1. $\downarrow\downarrow$ coronary heart disease.
2. Weight control.
3. Psychological satisfaction.
4. $\downarrow\downarrow$ insulin requirement ; the dose of insulin may be reduced 10- 15 % on the day of exercise .

C. Insulin therapy :**A. Insulin structure :**

- Insulin is small protein (MWT is about 5800) made of 2 polypeptide chain :
 - o A chain : 21 a.a.
 - o B chain : 30 a.a.
- Human insulin differs from porcine only at one amino acid at position No. 30 of (B) chain.
- Bovine insulin differ at two other sites amino acid 8 & 10 of the (A) chain.

B. Types of available insulin :

❖ Sources:

- 1) Pork
 - 2) Beef
 - 3) Human insulin
- a. Regular or crystalline insulin

- o Onset : 1/3 – 1 hour .
- o Peak : 2-4 hours.
- o Duration : 6- 8 hours.

b. Intermediate onset & duration :

- o Onset : 2 hours .
- o Peak : 4-12 hours.
- o Duration : 24 hours .
- o e.g : NPH , lente , mixtard , monotard .

c. Delayed onset & long duration :

- o these are not used in children below 6 years as they may cause night hypoglycemia , convulsions or death e.g. Insulin Glargin.

C. Regimens of insulin therapy :

- Two types of insulin regimens in routine use :
 - 1) Conventional therapy : (twice daily) .
 - 2) Intensive therapy (Multiple dose regimen)

1) Conventional therapy :

- a. Below 10 years .
 - b. Pregnant DM
 - c. Newly diagnosed who retained endogenous insulin secretion .
- Usually a combination of short + intermediate duration of insulin is used .
 - The total daily dose of insulin = $1/2 - 1$ unit / kg.

2/3 morning		1/3 evening	
2/3 NPH	1/3 crystalline	2/3 NPH	1/3 crystalline.

2) Intensive insulin therapy :

- a. Above 10 years .
 - b. Labile (brittle DM).
 - c. With rapid advancing tissue damage requiring near perfect glycemic control .
- 3-5 insulin injections / day .
 - Short acting before each meal & intermediate or long acting before bed time

D. Recent lines :

1) Insulin pump : $\rightarrow$ allow better control of blood glucose.

2) Pancreatic transplantation .

3) Trials therapy in newly diagnosed

IDDM :

a. Immune-modulator :

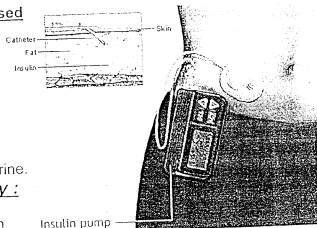
- IVIG.
- Plasmapheresis.
- Interferon.
- Thymic hormone.
- Levamisole.

b. Immune-suppressants:

- Cyclosporine + Azathioprine.

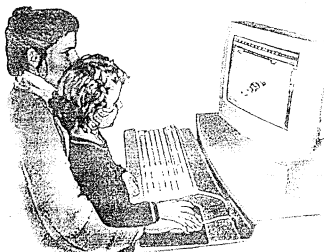
E. Complications of insulin therapy :

1. Hypoglycemia
2. Lipidystrophy at the site of injection.
3. Allergy & antibody formation .



D. Psychological management in IDDM:

- Patients need continuous balance between love & limits .
- Camps for diabetics to provide an enjoyable reaction , freedom & independence.



D.K.A.

- Keto-acidosis may be the initial presentation in 30 % of cases of IDDM.

Etiology

1. Missing doses of insulin.
2. Low dose of insulin.
3. Infection.
4. Stress.

G/P

1. Dehydration + Polyuria.
2. Metabolic acidosis: deep rapid respiration " Kausmol"
3. Cerebral deterioration ending in coma.
4. Acetone breathing.
5. Abdominal pain or rigidity may mimic acute appendicitis or pancreatitis.

Investigations:

1. Blood glucose > 300 mg/dl.
2. Ketonemia > 3 mMol/L (↑↑ B hydroxybutyrate & alpha acetoacetate.)
3. Metabolic acidosis :
 - $\text{pH} < 7.30$
 - $\text{HCO}_3^- < 15 \text{ mEq/L}$
4. Additional laboratory investigations
 - K + ECG → for hyperkalemia
 - If sepsis is suspected CBC, blood culture, urine culture.

Treatment:

It is a hospital emergency. the major lines of treatment are :

1. Correction of dehydration & electrolyte disturbance.
2. Correction of hyperglycemia.
3. Correction of acidosis.
4. Treatment of precipitating factors e.g infection.

A. Correction of dehydration :

Amount of fluid needed :

- 1st hour → 500 ml / m2.
- Next 2 hours → 500 ml / m2.
- Next 9 hours → 100 ml / kg.
- Next 24 hours → 2000 ml / m2.

OR :

- The total amount of fluid calculated in 36 hours can be given as follow :
 - 50-60 % in the first 12 hour
 - The remaining amount 40-50 % in the remaining 24 hours.

This policy aims at :

- Rapid refilling of circulation as management of shock.
- Then we reduce fluids to 1/2 to prevent encephalopathy, after which idiogenic osmoles disappear so that we can ↓↓ the rate.

Why oral intake is contraindicated before 36 hours ??

1. To rest the stomach " irritated by K+B "
2. Oral fluid modulator GIT hormones

B. Types of fluids :

- Start with normal saline.
- Once blood glucose $\rightarrow \leq 300$ mg % $\rightarrow$ give glucose 5% in normal saline.

C. Treatment of hyprglycemia :

- By insulin therapy as follows :
 - 1) **Short therapy** : 0.1 U / Kg IV shot.
 - 2) Then 0.1 U / Kg / Hr.
 - 3) When blood glucose reach ≤ 300 mg % $\rightarrow 0.05$ u/kg/hr.

D. Treatment of acidosis :

- If PH $> 7.2 \rightarrow$ no correction
- If PH $< 7.2 \rightarrow$ correction according to bicarbonate deficit in blood gases.

E. Treatment of infection :

- Broad spectrum antibiotics.

Complication during treatment :

1. Hypokalemia or hyperkalemia .
2. Hypoglycemia
3. Hypocalcemia
4. Over whelming infection.
5. Irreversible fatal cerebral edema or Hge.

D.D of DKA :

1. From other causes of coma as non-ketotic & hypoglycemic coma.
2. Complicated gastroenteritis
3. Uremia
4. Lactic acidosis.
5. Salicylate intoxication.
6. Encephalitis & intra-cranial lesions.
7. Pneumonia.

Post acidotic phase or transition period for establishment of metabolic control

- ❖ DKA usually corrected within 36-48 hours . then at the transition stage SC crystalline insulin are begun at a dose of 0.1-0.25 U/Kg every 6-8 hours, before meals with simultaneous monitoring of the blood glucose & adjustment of insulin dose for 1-2 days .
- ❖ The aim of therapy during the transitional period are to treat any recognized precipitating cause of DKA such as infection , to stabilize the patient metabolic control by adjusting the insulin dose .

Dwarfism

- Normal growth is the expression of :
 1. Hormonal factors
 2. Environmental factors
 3. Nutritional factors
 4. Genetic factors

Types :

A. Proportionate :

- Whole body is proportionately affected e.g. : pituitary dwarfism.

B. Disproportionate

- Lower segment is more affected than upper segment & span is more affected than height.

Genetic height potential :

- It is the expected adult height in normal persons .
- It can be calculated from the mid-parental height " height of father + height of mother / 2 " as follows:
 - 1) Add 6.5 cm to mid-parental height in case of boys.
 - 2) Subtract 6.5 cm from mid-parental height in case of girls.
 - 3) The genetic height potential is ± 8 cm

Causes of dwarfism :

❖ Primary disorders

i. Disproportionate short stature :

- Skeletal causes :
 - 1) Achondroplasia : short limbs & normal trunk.
 - 2) Osteogenesis imperfecta : fragile bones $\rightarrow$ multiple fractures $\rightarrow$ mal- union dwarfism .
 - 3) Pott's disease of spine.
- Congenital error of metabolism:
 - 1) MPS.
 - 2) Rickets .

ii. Dysmorphic features :

- Syndromes with chromosomal aberrations :
 - 1) Turner's syndrome .
 - 2) Down syndrome.
- Syndromes without chromosomal aberrations :
 - 1) Silver Russell syndrome.
 - 2) Noonan syndrome.

❖ Secondary disorders :

i. Nutritional diseases and malabsorption :

- 1) Poor weight gain usually occurs before short stature is noticed .
- 2) Characteristic features of malnutrition .

ii. Endocrinal diseases :

1. Cretinism
 - o Disproportionate dwarfism
 - o Characteristic features of cretinism
2. Pituitary dwarfism
 - o Due to $\downarrow\downarrow$ GH.
 - o Proportionate dwarfism
3. Loran syndrome:
 - o Due to $\downarrow\downarrow$ somatomedins (IGFs).
4. Frohlich syndrome:
 - o Trunkal obesity
 - o Hypogonadism
 - o Genu-valgus.
5. Precious puberty
 - o Premature fusion of epiphysis .
6. Cushing disease or syndrome.
7. Diabetes mellitus .
8. Pseudo-hypoparathyroidism.

iii. Chronic illness.

1. Severe heart disease.
2. Chronic infection & toxemia.
3. Liver cirrhosis & lipid storage disease.
4. Chronic nephritis & DM.

iv. Iatrogenic short stature

- Chronic steroid therapy.

v. Psychogenic short stature:

- Emotional deprivation.
- Anorexia nervosa.

❖ Normal variant or idiopathici. Familial :

- The patient has short parents.
- There is normal growth velocity & normal bone age.

ii. Constitutional :

- Here , there is normal growth velocity.
- Bone age & puberty are delayed.
- Typically there are :
 - 1) Normal at birth , with normal growth till 6 months.
 - 2) Then : growth becomes very slow till 2 years age " <5th percentile ".
 - 3) Then there is normal growth velocity " growth curve is parallel to that of 5th percentile "
 - 4) Growth continues for a longer time than normal " due to delayed puberty " $\rightarrow$ so height becomes normal again .
 - 5) Family history is usually +ve.

Investigations:

1. CBC :

- Chronic anemia , infection.

2. ESR :

- Collagen diseases.
- Chronic infection as T.B .

3. Urine analysis :

- Pyelonephritis.
 - Glomerulo-nephritis.
 - Renal tubular disease.
- e.g : Fanconi syndrome , lignac syndrome , Lowe syndrome.

4. Stool :

- Parasitic infestation.
- Occult blood – undigested food.

5. Renal function test.

6. Karyotyping.

7. Thyroid functions.

8. GH & somatomedins

Treatment:

Depends on the cause:

1. Familial → no treatment.
2. Constitutional → re assurance .
3. Cretinism → see later.
4. Pituitary dwarfism → GH.
5. Turner syndrome → GH + sex hormone.
6. Treatment of chronic disease

Growth hormone

- GH is an anterior pituitary hormone.
- It's release is controlled by 2 hormones , GHRH which is stimulatory & somatostatin which is inhibitory.
- It induce linear growth directly & indirectly by inducing insulin like growth factor 1 (IGF-1) secretion by the liver.

Causes of GH deficiency:

1. Birth trauma.....Ichge in the pituitary fossa.
2. Hereditary.....due to genetic defect.
3. Congenital developmental anomalies.
4. Inflammatory.
5. Cranial irradiation.
6. Craniopharyngioma.
7. Histiocytosis.
8. Maternal deprivation.

Investigations:

- 1) GH assessment: $< 10 \text{ ng / ml}$ is diagnostic.
- 2) Provocation test: by insulin or clonidine.

Treatment:

Recombinant GH: $15\text{-}20 \text{ IU / m}^2 \text{ / week}$, divided into 3-6 doses SC at bedtime.

Tall stature

Definition:

$> 95^{\text{th}}$ percentile or $> 2 \text{ SD}$ above the mean for age & sex.

Causes:

1. Familial.
2. Endocrinal.
 - o Pituitary gigantism.
 - o Hypogonadism.
 - o Precocious puberty in 1st school.
3. Chromosomal:
 - o XXY.
 - o XYY.
 - o XXX.
4. Others:
 - o Marfan S.
 - o Homocystinuria.
 - o Cerebral gigantism. (SOTO S).
 - o Simple obesity.

Cretinism

Definition:

It is congenital hypothyroidism i.e: occurring since birth.

Causes:**A. Permanent:**

1. Congenital absence or hypoplasia of thyroid gland.
2. Congenital defect.
 - TSH receptor defect.
 - Iodine trapping defect.
 - Organification defect.
 - Iodotyrosine deiodinase deficiency.
 - Thyroglobulin defect.

$\downarrow \downarrow$ thyroxin level $\rightarrow \uparrow \uparrow$ TSH $\Rightarrow$ Goiter.
3. Endemic cretinism $\rightarrow$ due to iodine deficiency.
4. $\uparrow \uparrow$ use of anti-thyroid drugs or radio-active iodine during pregnancy.
5. 2nd hypothyroidism $\rightarrow$ hypopituitarism.
6. Tertiary hypothyroidism $\rightarrow$ hypothalamic function.

B. Transient :

1. Maternal ingestion of goitrogenic substances
 - o Iodine (cough expectorant)
 - o Anti-thyroid drugs.
2. Maternal iodine deficiency .
3. Maternal transfer of TSH receptor blocking antibodies.
4. Neonatal use of iodine antiseptics.

**A. General features :****1. Face:**

- 1) Low anterior hair line.
- 2) Puffy eye lids.
- 3) Depressed nasal bridge.
- 4) Big lips.
- 5) Large protruded tongue.
- 6) Delayed dentition.

2. Hands:

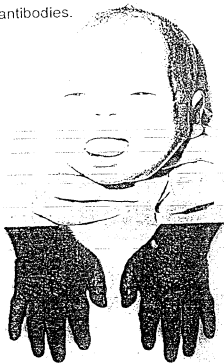
- 1) Short tapering fingers.
- 2) Square shaped.
- 3) Dorsal pad of fat.

3. Disproportionate dwarfism:

The height is more than the span.

4. Delayed walking & waddling gait.

Due to dysgenesis of the femur head muscle weakness.

5. Subnormal body temperature.**B. Skin manifestations:**

1. Dry, rough , scaly, cold skin.
2. Hair is scanty , coarse & brittle.
3. Deposition of S.C myxoedematous tissue, particularly on the dorsum of hands , face & subclavian regions.

C. Nervous manifestations :**1. MR :**

- o Delayed motor milestones.
- o Delayed talking.
- o Delayed sphincteric control.

2. Hoarse cry**D. Cardiovascular manifestations :**

1. Bradycardia.
2. ECG $\rightarrow$ low voltage.

E. Muscle weakness:

1. Pot belly abdomen.
2. Umbilical hernia.
3. Constipation.

F. Early manifestations:

1. Over weight baby .
2. Prolonged physiological jaundice.
3. The baby sleeps much , cries little & feeds little.
4. Delayed closure of posterior fontanel.

5. Abdominal distention, constipation & umbilical hernia.
6. Hoarse cry.

N.B: Examination of the neck is very important to exclude thyroid swelling.

Investigations:

A. Hormonal assay :

1. In 1ry hypothyroidism :
 - o $\downarrow\downarrow$ T3, T4 " N:4-9 ug/dl"
 - o $\uparrow\uparrow$ TSH " N:2-10 U/L"
2. In 2ry & 3ry hypothyroidism :
 - o TSH is low

How to differentiate between them ?? by TRH stimulation test :

- a) If $\rightarrow$ $\uparrow\uparrow$ TSH = tertiary hypothyroidism .
- b) If $\rightarrow$ no response = 2ry hypothyroidism.

B. Serum cholesterol level $\rightarrow$ $\uparrow\uparrow\uparrow$

C. ECG $\rightarrow$ low voltage + sinus bradycardia.

D. X-Ray :

1. Delayed bone age.
 - o At birth $\rightarrow$ absent distal femoral epiphysis.
 - o Later $\rightarrow$ delayed appearance of carpal bone.
2. Epiphyseal dysgenesis:
 - o Affecting head of femur & humerus.
3. Beaking of T12 & L1,2 vertebrae.
4. Intra-suture bone in skull $\rightarrow$ Wormian bone.

E. Others :

1. Thyroid scan.
2. Thyroid biopsy.
3. Thyroid antibodies.

D.D:

From other causes of mental & growth retardation e.g. : Mongol & MPS.

Treatment:

- Hormonal replacement therapy for life :

L-thyroxin tab $\rightarrow$ 4 ug / kg / d then gradual increase the dose according to clinical & laboratory response.

- 1) GIT $\rightarrow$ constipation or diarrhea.
- 2) Pulse $\rightarrow$ $\downarrow\downarrow$ or $\uparrow\uparrow$
- 3) Appetite
- 4) Growth in weight and height.

N.B Pendred syndrome:
deafness, goiter.

Prognosis:

- The prognosis depends upon:

- a. Early diagnosis and treatment.
 - b. Severity of thyroid hormone deficiency.
1. Cases treated before 3 months $\rightarrow$ very good prognosis for mentality.
 2. 3-6 months $\rightarrow$??
 3. After 6 months $\rightarrow$ poor mentality.

Juvenile Myxedema

- It is acquired hypothyroidism during childhood.

Etiology :

- 1) Autoimmune thyroiditis.
- 2) Surgical removal of thyroid gland.
- 3) Ingestion of goitrogenic substances.
- 4) Endemic iodine deficiency.
- 5) 2ry or 3ry due to tumor , trauma , infection or irradiation.

Treatment:

- As cretinism.